REMARKS

The Office Action of September 25, 2001 presents the examination of claims 1-10, 14, and 15. Claims 1, 3, 14, and 15 are amended. No new matter is inserted into the application.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 1-10, 14, and 15 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Claims 1, 14, and 15

The Examiner maintains her argument that the recitation of "all exons...which encode biologically functional domains" is unclear. However, the Examiner notes that this rejection would be obviated if step a) is amended to read "determining the nucleotide sequence of exons 2-11 of a cancer-related p53 nucleic acid derived from a human neoplastic tissue or body fluid." In response to the Examiner's remarks, Applicants amend the claims as suggested. Thus, the instant rejection is overcome.

Claims 1 and 14

The Examiner asserts that step d) of claims 1 and 14 is unclear for allegedly not correlating to the preamble of the claims. In response to the Examiner's remarks, Applicants amend the claims to recite that the development of the neoplasia is prognosticated by combining the results of steps c)(i) and c)(ii). Thus, the instant rejection is overcome.

Claim 3

The Examiner asserts that claim 3 is newly indefinite because the amended claim 3 removes reference to the "type" of mutation in line 3, but is still drawn to a method of categorizing the aggressiveness of the cancer based upon the "type" in line 6. In response to the Examiner's remarks, Applicants amend claim 3 to reinsert the term "type" in line 3 such that the claim is fully clarified. Thus, the instant rejection is overcome.

Based upon the above, Applicants respectfully submit that the amended claims fully comply with 35 U.S.C. § 112, second paragraph. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner maintains the rejection of claim 3 under 35 U.S.C. § 112, first paragraph for allegedly not being described in the specification. Applicants respectfully traverse. Reconsideration of the claim and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner states that Applicant's arguments are unpersuasive because a basis for correlating a specific type of mutation with cancer outcome has allegedly not been demonstrated. Applicants respectfully disagree.

First, on page 3, lines 9-19, it is stated that approximately 70% of mutations in p53 are missense mutations that change the identity of an amino acid and alter the confirmation and stability of p53. It is well known in the art that a missense mutation is a change in a codon that results in an amino acid change in the corresponding protein. These amino acid changes, in the case of p53, result in an alteration of the sequence specific DNA binding and transcription factor activity of p53.

Further, on page 7, lines 32-38, it is stated that mutations in p53 that give rise to transcriptional stop signals and a truncated protein prevent p53 from employing its DNA

proof-reading role. It is well known in the art that early transcriptional stop signals can be the result of a frameshift mutation, which change the reading frame of the mRNA, or a nonsense mutation, which is a mutation that creates a premature stop codon within a gene's coding region, such as amber mutations (UAG), ochre mutations (UAA), and opal mutations (UGA).

Finally, on page 8, lines 3-10, it is stated that mutations detrimental to the patient are those which affect the DNA binding or transactivation, whereas those mutations less harmful for the patient are amino acid changes not greatly affecting structure or function of p53. Thus, it is clear to the skilled clinician that a frameshift or nonsense mutation would be more detrimental to a cancer patient, whereas a missense mutation would be less detrimental to the cancer patient.

Thus, contrary to the Examiner's assertions, the prognosis of neoplasia based on the "type" of mutation is indeed described in the specification so as to reasonably convey to one skilled in the art that the present Inventors had possession of the claimed subject matter at the time of filing. Further, Applicants amend claim 3 to recite that a mutation in a conserved region II and V of p53 is indicative of poor patient

outcome whereas a mutation in a conserved region III and IV is indicative of positive patient outcome, thus completely clarifying the subject matter recited therein.

As these amendments and remarks address and overcome the issues of written description raised by the Examiner, Applicants respectfully request withdrawal of the instant rejection.

Rejection under 35 U.S.C. § 102(b)

The Examiner maintains the rejection of claim 15 under 35 U.S.C. § 102(b) for allegedly being anticipated by Thorlacius et al. (*Cancer Res.*, 53:1637-1641 (1993)). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Thorlacius et al. discloses the DNA sequencing of exons 5, 7, and 8 to determine p53 mutations. The instant claim 15 is amended to recite that the nucleotide sequence of exons 2-11 of a cancer-related p53 nucleic acid derived from a human neoplastic tissue or body fluid is determined in step a). Thorlacius et al. fails to disclose a method for prognostication of the development of neoplasia by sequencing exons 2-11 of p53.

For these reasons, Thorlacius et al. fails to anticipate the present invention. Withdrawal of the instant rejection is

therefore respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 2, 4-10 and 14 under 35 U.S.C. § 103(a) over Hedrum et al. in view of Elledge et al. and Callahan et al., for reasons of record. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

As stated above, the claims are amended to recite that the nucleotide sequence of exons 2-11 of a cancer-related p53 nucleic acid derived from a human neoplastic tissue or body fluid is determined in step a). Elledge et al. and Callahan et al. fail to detect p53 mutations by sequencing exons 2-11 of the gene. Again, the Examiner attempts to make up for the deficiencies of Elledge et al. and Callahan et al. by adding Hedrum et al. However, Hedrum et al. merely teaches the sequencing of exons 4-9. Thus, absolutely no reference teaches a method for prognostication of the development of neoplasia by sequencing exons 2-11 of p53.

Finally, with respect to claim 10, the Examiner asserts that the claim no longer refers to the complete coding region of p53. However, this statement is incorrect because claim 10 is

dependent from claim 1, which references the sequencing of exons 4-11 of p53.

As such, the present invention is not unpatentable over the combination of references cited by the Examiner. Withdrawal of the instant rejection is therefore respectfully requested.

New rejections under 35 U.S.C. §§ 102, 103

The Examiner rejects claim 15 under 35 U.S.C. § 102(e) for allegedly being anticipated by Vogelstein '676 (USP 5,527,676). The Examiner also rejects claims 1, 2, 4-10, and 14 under 35 U.S.C. § 103(a) for allegedly being obvious over Vogelstein '676, in view of Elledge et al. and Callahan et al., and further in view of Hedrum et al. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Vogelstein '676 discloses a method for assessing mutations and/or loss of p53 gene in human tumors. Claim 3 of Vogelstein '676 recites that the loss of wild-type p53 genes is detected by sequencing all or part of the p53 gene. The Examiner asserts that the instant claims read on "determining the entire coding sequence of p53." As stated above, however, the amended claims recite that the sequence of exons 2-11 of p53 are determined.

However, Vogelstein '676 fails to disclose sequencing the specific exons 2-11. Thus, Vogelstein '676 fails to anticipate the present invention.

Further, Elledge et al. and Callahan et al. fail to detect p53 mutations by sequencing exons 2-11 of the gene, whereas Hedrum et al. merely teaches the sequencing of exons 4-9. Thus, absolutely no reference teaches a method for prognostication of the development of neoplasia by sequencing exons 2-11 of p53.

As such, the present invention is not unpatentable over the combination of references cited by the Examiner. Withdrawal of the instant rejection is therefore respectfully requested.

Summary

Overall, the present invention possesses significant patentable features that the cited prior art references do not possess. Furthermore, Applicants submit the instant claims are fully in compliance with 35 U.S.C. § 112, first and second paragraphs. All of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Favorable action on the merits of the present application is thereby requested.

For any matters that can be resolved through a telephone discussion, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the law offices of Birch, Stewart, Kolasch & Birch, LLP, (703) 205-8000, in the Washington, D.C. area.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____

Gerald M. Murphy, Jr.
Reg. No. 28,977
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the following claims:

1. (Six Times Amended) A method for prognostication of the development of neoplasia and providing guidance for treatment in a human patient having a neoplasia comprising:

a) determining a nucleotide sequence of [all] exons 2-11 of a cancer-related p53 nucleic acid [which encode biologically functional domains from genomic DNA or cDNA] derived from a human neoplastic tissue or body fluid;

b) analyzing the nucleotide sequence determined in step a) for the presence of mutations; and

c) classifying the neoplasia into different subgroups depending on

(i) the presence or absence of a mutation, and

(ii) whether the patient is node positive or not; and

d) prognosticating the development of the neoplasia by combining the results of steps c)(i) and c)(ii) wherein said results are indicative of patient survival and providing guidance for the treatment of the patient.

3. (Three Times Amended) The method of claim 2, further comprising determining the presence, [and] position, and type of

[the] mutation and categorizing biological aggressiveness and/or metastatic potential of the neoplasia based upon the presence, position, and type of mutation,

wherein said neoplasia is breast cancer,

and wherein a mutation in a conserved region II and V of p53 is indicative of poor patient outcome whereas a mutation in a conserved region III and IV is indicative of positive patient outcome.

14. (Four Times Amended) A method for prognostication of the development of neoplasia in a human patient having a neoplasia comprising:

a) determining the nucleotide sequence of [all] exons 2-11 of a cancer-related p53 nucleic acid [which encode biologically functional domains from genomic DNA or cDNA] derived from a human neoplastic tissue or body fluid;

b) analyzing the nucleotide sequence determined in step a) for the presence of mutations; and

c) classifying the neoplasia into different subgroups depending on

(i) the presence or absence of a mutation, and

(ii) whether the patient is node positive or not; and

d) prognosticating the development of the neoplasia by combining the results of steps c)(i) and c)(ii), wherein said results are indicative of patient survival.

15. (Four Times Amended) A method for prognostication of the development of neoplasia in a human patient having a neoplasia comprising:

a) determining the nucleotide sequence of [all] exons 2-11 of a cancer-related p53 nucleic acid [which encode biologically functional domains from genomic DNA or cDNA] derived from a human neoplastic tissue or body fluid;

b) analyzing the entire nucleotide sequence determined in step a) for the presence of mutations; and

c) classifying the neoplasia into different subgroups depending on the presence or absence of a mutation; and

d) prognosticating the development of the neoplasia by analyzing the results of step c) only, wherein said results are indicative of patient survival.